(1) Occupational Cancer

Since the observation in 1775 that the incidence of scrotal cancer was unusually high in chimney sweeps, our knowledge of environmental cancer in man has been chiefly based on studies of occupational groups with unusually high cancer rates. Our knowledge of such factors as latent period, dose response, and relation of types of cancer to environmental agents has been based on detailed studies of occupational cancer. More recently, similar data on the environmental aspects of lung cancer have been obtained in the general population with investigation of such factors as cigarette smoking and air pollution as causal agents. A partial list of occupations as they pertain to cancer of the lung follows:

Radioactive or mining and smelting
Coke oven operators
Gas works operators
Chromium ore refining
Nickel ore refining
Asbestos mining and use
Welders, Steam fitters, Short order cooks,
Crane operators, Foundry workers

At present, occupational cancer offers two additional unique opportunities for research. (1) The growth in number, efficiency, and reliability of hospital cancer registries, state tumor registries, as well as a most laudable spirit of willingness and cooperation on the part of industry (private corporations as well as nationwide trade associations) makes it now appear feasible to determine the actual contribution of occupational cancer to the total cancer spectrum in the United States. The increment represented by occupationally determined or occupationally caused cancers may be as little as 2 to 5% or as much as 35 to 50%. We do not know. Because we are aware of this and since correction of occupational cancer environments has thus far been the most effective means of cancer control, a long-term study to determine its actual significance seems timely and important. Further, the study will inevitably contribute to our more accurately assessing the role of non-occupational environmental factors and cancer. (2) The second opportunity provided by studies in occupational cancer is that persons at higher risk to cancer of any site because of occupational experience make up prime population groups for fundamental studies on the pro-neoplastic and pre-neoplastic states. The former term describes individuals at higher risk to cancer because of the specific environment in which they work; the latter describes individuals who in addition to being in a high risk environment have certain pathological or other biological stigmata indicating the earliest stages of tissue reactions including benign lesions which may progress to overt cancer. Such patients can be studied using such recent, important, and relevant techniques of cytogenetics (chromosomal studies for the presence of abnormalities which may herald an oncoming cancer), biochemistry in which metabolic abnormalities in target organ sites may be identified by enzymes and other protein studies, and histopathological, histochemical and electron microscopic studies of cells from organ or organ systems at high risk.

(2) Double Primary

An exciting and potentially very useful tool in studying the causes of cancer is the growing recognition and supporting evidence that a person with a previously diagnosed, successfully treated cancer is at greater risk to a second, independent primary cancer than appropriate controls. Recently, the successful treatment of cancer has permitted patients to survive long enough to develop a second cancer. This development of a second tumor is of critical importance as it may well indicate a systemic factor in susceptibility to cancer induction. Though this has long been suspected, this appears to be the first time we have the availability of model systems to study this important problem. For example, a patient with oral cancer who has been treated and cured is perhaps at fifty times the risk to esophageal cancer compared to appropriately selected controls. Similarly, increased risk to visceral cancer (cancer of internal organs) has been observed in patients with cancer in situ of the skin. Associations of this kind permit the use of these patients for fundamental biochemical, physiological, and pharmacological studies of the pro-malignant or pre-malignant state as noted above under occupational cancer.

(3) Metabolic Approach to Epidemiologic Observations on Selected Populations

Just as it has been long known that during an epidemic of an infectious disease not all of the exposed population succumbs, so in high risk cancer environments not all of the exposed develop cancer. For infectious diseases, an immunologic basis for patterns of residence and susceptibility appear to account for the epidemiologic observations. In neoplastic disease, a possible explanation may reside in the capability of the host to metabolize, detoxify and excrete environmental carcinogens. Specifically, one may ask, "Why by far do most of those two-pack-a-day, twenty-year cigarette smokers not develop lung cancer?" The explanation is most complex and certainly involves such factors as intensity and duration of exposure (dose), age at onset of exposure, and frequency of intervals of exposure as well as host factors which appear to be operative in establishing "susceptibility" and "resistance." Pertinent and relative to this is the observation that populations migrating from country to country as well as from rural to urban areas significantly alter their risk to cancer of virtually all sites. For cancers of some sites, they adopt the risk pattern and mortality rates of the country to which they have immigrated. For others, they retain the pattern of the country from which they emigrated. This can be manifested by either an increase or decrease in risk to cancer of a certain, specific site.

I believe we are ready to investigate the possible metabolic bases for these differences in susceptibility and alterations in risk. Environmental carcinogens do not differ essentially from other environmental, toxic agents in that they too have to undergo metabolic change in the body either for the

purpose of detoxification or, in a few diabolical instances, actual formation of the active carcinogen in the host through metabolic transport of the environmental agent. These metabolic changes are accomplished by enzymes which fall into several categories. Of primary concern to us is the class of enzymes referred to as "induced" enzymes. These are formed in the body in response to the introduction of a foreign agent. The function of the enzyme is to alter or activate the carcinogenic agent presumably though not always to the benefit of the host. The ability of these enzymes to perform their function of neutralizing or detoxifying carcinogens is a "learned" biological experience analogous to the production of antibodies to ragweed, pollen, horse hair, bacteria, or infectious agents. Not all people appear to possess the same ability to respond to the stimulus for enzyme formation. Differences are exaggerated in the presence of abnormalities in the major, enzyme-forming tissues. The liver is one of the major sites of enzyme formation for the metabolism of chemical carcinogens. Anything interfering with normal liver function presumably from mild insults ("x" number of martinis) to severe insults (hepatitis and cirrhosis) interferes with the liver capabilities to produce enzymes. Other environmental insults aimed at different anatomic sites can interfere with the ability of the cells of the lung, the cells of the stomach, the cells of the kidney, etc., etc., to form enzymes in response to stimuli. The number of agents and factors that can interfere with liver function or the function of other organs is great. The significance of this biological phenomena in determining the susceptibility of man to cancer is ready for investigation through the use of laboratory models having a high degree of relevancy to man. Our knowledge of comparative biochemistry, pathology, and pharmacology has progressed so that meaningful extrapolation of experimental data to man is becoming more and more assured. A potential, long-term goal of such studies is the more than theoretical possibility of artificially buffering or protecting the various organs against enzyme-neutralizing or enzyme-destroying environmental substances, or conversely, artificially stimulating enzyme systems so that they can competitively neutralize carcinogens at the cellular level.

(4) Anticarcinogenesis As Means for Investigating Mechanisms for Carcinogenesis and Cancer Prevention

Chemical carcinogens are introduced into the general environment as constitutents of complex mixtures. Several carcinogenic agents are present simultaneously: In cigarette smoke, auto exhaust, industrial effluents, and polluted urban air, for example, in addition to the carcinogens, numerous structurally-related non-carcinogenic compounds are usually emitted into the environment as part of the pollutant mixture. These combinations of related compounds (Isomers - same chemical composition but structurally different; and Analogues - similar but not identical in chemical composition and structure) react with one another as well as with the host system they are attacking. It has been shown that carcinogenic potency of these environmental agents is

significantly related to the ratio of these various compounds to one another. Experimentally, it has been possible, through purposefully altering the ratio of these compounds to one another, to eliminate carcinogenic potency without the necessity of laboriously eliminating the carcinogenic constituents of a mixture. In essence, the carcinogens in the environment are drowned. The implications for this in the control of sources of environmental carcinogens are great. The mechanism of the "anticarcinogenic effect" is not completely understood though we have learned more about it in the last few years than the preceding decades. This area is ripe for exploitation. Its ultimate goal in terms of cancer control is the ability to intentionally alter and control ratios of the various compounds to one another to make sources of carcinogens less hazardous or completely free of hazard. One can only guess whether "safe polluted urban air" or "a safe cigarette" is possible. If this is a tenable hypothesis, and I would guess that there is better than a 50-50 chance that this is so, the approach suggested here is promising. From a host viewpoint, anticarcinogenesis is also a potentially fruitful approach for the study of basic mechanisms as well as application to cancer control in those organ or organ systems that are targets for environmental carcinogens which may be buffered or protected using the anticarcinogenesis principle.

(5) Familial Cancer and Association of Cancer and Congenital Abnormalities

The role of genetics or heredity in the Mendelian sense in susceptibility to cancer is really unknown; nevertheless, several recent observations can contribute to our ability to assess the role of inheritance through the study of defined populations with unique patterns of cancer incidence.

It has been shown that for cancer of specific sites, certain families have higher rates than expected. For instance, cancer of the urinary bladder has been shown to occur at a fantastically higher rate in several members of a few families whose genealogies have been studied. Further, these families have abnormalities in the metabolism of an amino acid, tryptophane, which in experimental studies has been shown to be concerned with the pathogenesis of urinary bladder cancer. The extent and universality of "errors in metabolism" in relation to cancer is unknown. It may be of overwhelming significance or quite unimportant. Nevertheless, we know for instance that major errors in metabolism can result in such non-cancerous disease as phenylketonuria and galactosemia, cystinuria, etc. The question is: "Could the lower, more subtle level of errors in amino acid, carbohydrate, or fat metabolism be manifested over the long period by susceptibility to cancer?" The ability to study large populations and the more recent capability of designing experiments predicated on epidemiologic and biometric observations can assure meaningful studies of the role of genetic factors in cancer at this time.

It has been shown that the congenital abnormality, mongolism, is associated with an increased risk to leukemia in children (Down's Syndrome). More recently studies have shown that a whole series of congenital abnormalities are associated with increased risk to other cancers, as for example, Wilm's tumor of the kidney. One may ask if indeed congenital abnormalities

and cancer are the results of the same environmental agents with different clinical manifestations since, in the former, it is the embryo and fetus that are attacked while in the latter, it is the fully developed individual. A new approach to the study of cancer causation, therefore, appears feasible for it is known that if two diseases appear to be etiologically related the more that we learn about one, the more we inevitably know about the second. Controlled experimental and laboratory studies and populations in this area can now be undertaken.

(6) Natural Product Carcinogenesis

It is understandable that a society investigating disease patterns which appear temporally related to man-made changes in the environment would assume that the recent changes may be responsible for the new or unique patterns. We have recently become aware, however, of the ever-growing importance of environmental carcinogens that are the product of natural agents. These include certain botanical substances and food stuffs as well as what may be more important at present, infectious agents such as fungi. These latter agents produce the most potent chemical carcinogens we know. They are worldwide in their distribution and, more important perhaps, they begin to offer a partial explanation for historically unique cancer patterns in non-industrial or underdeveloped parts of the world. The actual combination of natural product carcinogens to the total cancer spectrum in the United States is unknown. Suffice it to say, they have been identified in the United States and the recent experience with cancer of the liver in trout appears to be attributable to a natural product contaminating synthetic diets used in the feeding of fish in commercial hatcheries. It now appears imperative to devote as much attention to these natural products as we do to man-made carcinogens.

Investigations in the foregoing areas require close and intense cooperation between the National Cancer Institute and a virtually unlimited number of universities, research institutes, and laboratories in private industry. The central role of the National Cancer Institute is apparent in view of its accessibility to vital records primarily located in government bureaus as well as its accessibility to industry on a nationwide basis. These records provide much of the required base for epidemiological and biometric studies.

The implementation of these studies would, of course, have to be on a basis of successive phases and would probably require as long as a decade for the benefits to be measured in terms of hopefully reducing cancer risks, rates, as well as increasing survival.